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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,769	10/25/2000	Darwin J Prockop	9598-101U2(99-0356)	4022

7590 03/24/2005

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,769	PROCKOP ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-29,31-36,* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-29,31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the First Action on the Merits filed on December 27, 2004 is acknowledged.

Claims 1, 16, 24, 31, 32 have been amended. Applicants have correctly pointed out that claim 13 was cancelled in the Amendment filed April 19, 2004.

Claims 1-12, 14-29, 31-36 are under consideration.

Maintained Rejections

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-12, 14-29, 31-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al. (1997, Biotechnology Letters, 19: 89-92) for reasons of record set forth in the previous Office Action, August 10, 2004.

The instant invention is to a method of propagating human bone marrow stromal cells plated at low density.

Examiner's Response

Applicant's arguments filed December 27, 2004 have been fully considered but they are not persuasive.

The instant invention is to a method of propagating human bone marrow stromal cells plated at low density. Huang et al. teaches a method in which murine bone

marrow cells were propagated at low density. The question at hand is whether Huang et al. anticipate the instant invention.

The rejection is maintained for the following reason. While the bone marrow stromal cells were obtained from different animals, an artisan would not expect bone marrow cells from a mouse to behave any differently from any other mammalian bone marrow cells in methods of propagating cells. In the event that the claimed methods are not identical to those disclosed by Huang, et al., it is considered that any differences would be the result of minor changes, wherein such changes would have been obvious over the prior art. Thus, the claimed invention as a whole was at least prima facie obvious over, if not anticipated by, the prior art. Unless the Applicant provides substantial evidence to the contrary, the rejection remains. It is reiterated that the claimed invention is drawn to a method that has the same steps at taught by the prior art of record, even though the art of record used mouse cells and the claimed invention used human cells. Changing the source of the cells does not materially change the steps of the method.

Claims 1-12, 14-29, 31-36 remain rejected under 102(b) for the reasons discussed above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, 14-29, 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (1997, Biotechnology Letters, 19: 89-92) for reasons of record set forth in the previous Office Action, August 10, 2004.

The instant invention is to a method of propagating human bone marrow stromal cells plated at low density.

For the reasons discussed above in the 102(b) rejection, the 103(a) rejection remains.

Examiner's Response

Applicant's arguments filed December 27, 2004 have been fully considered but they are not persuasive.

With regards to the issue that Huang et al. do not teach plating and replating (Applicant's response, page 11, 1st parag.), the Applicant does not provide evidence to the contrary why an artisan would not use the methods taught by Huang et al. in replating and expanding cells. Huang et al. teach that of the stromal cell lines obtained LC1, LC2, and LC3, none was able to proliferate from a single cell in 3 weeks. The result indicated that there was a minimum initial cell density that is required for cell growth (Huang, et al., page 90, 1st col., 4th parag). Huang et al. teach that the one reason for the requirement for cells to be plated at high density stems from the fact that there needs to be an adequate concentration of an essential soluble growth factor. Huang et al. teach that in the case of macrophages, that factor was M-CSF (page 90,

2nd col., 2nd parag). In other words, while there is a need for high density plating, in some cases, the need for high density plating can be overcome for cells plated at low density by adding growth factor to the medium. Huang et al. teach that media collected from confluent dishes containing LC1, LC2, or LC3 cells (i.e. "conditioned media") were added to media of 50 cell/well cultures. Huang et al. teach that 50 cell/well LC3 cells responded to conditioned media obtained from confluent LC1, LC2, and LC3 cells (Huang, et al., page 91, 1st col, 2nd parag). LC2 cells plated 50 cells/well responded to conditioned media from LC2 and LC3 cells, and not as well to media from LC1 cells (Huang, et al., page 91, 1st col., 3rd parag). LC1 cells did not respond to any of the conditioned media. Despite the result for LC1 cells, Huang et al. teach that some factor(s) stimulated cell proliferation in sparsely seeded cell cultures (Huang et al., page 91, 1st col., 2nd parag., lines 6-8), as seen in LC2 and LC3 cultures. Despite the Applicant's argument that Huang et al. do not teach plating and replating at specific cell densities to arrive at expansion levels encompassed in the Applicant's application, an artisan, based on Huang's result would reasonably expect that replating LC2 and LC3 cells at low density in the presence of conditioned media would result in cell proliferation. Thus, despite Huang et al. teaching that the initial plating of the cells was higher than that that of the instant invention (Applicant's response, page 13, 2nd parag.), the problem is overcome when Huang et al. use conditioned media.

With regards to the argument that Huang et al.'s invention teaches cell proliferation was seen in cells treated with MPA (Applicant's response, page 14, 1st parag.), whereas the Applicant's cells of the instant invention are not treated with MPA,

the Examiner points the Applicant to Huang et al.'s LC2 line, which was not treated with MPA and grew in the presence of conditioned media (Huang, et al., page 91, 1st col, 3rd parag.) Thus, while the MPA treated cell may not be consistent with the teachings in the specification as filed, Huang et al. does teach that LC2 is not treated with MPA and would thus be similar to the cells of the instant invention.

With regards to the argument that Huang et al. "at best,... teaches the use of conditioned medium to generate colony formation during non-passage culturing (Applicant emphasis) of murine bone marrow stromal cells at initial densities of 50 cell/well (24 well plates) for MPA-treated cells. As such, the teachings of Huang would motivate one skilled in the art to use conditioned medium over growth medium to enhance the proliferation of the cells without replating the cells at the low densities of the present invention (Applicant's response, page 14, 2nd parag., lines 16-21)," it should be pointed out that Huang et al. teachings do not provide instances to the contrary that an artisan could practice the instantly claimed invention using Huang's methods. First, Huang et al. teach that LC2, a non-MPA treated cell line, could respond to conditioned medium. Second, Huang et al. teach that the limiting factor for sparsely seeded cells to proliferate appeared to stem from the fact that there was no growth factor(s) in the media. Huang et al., showed that after being seeded to 50 cells/well (which involves steps of cell dissociation and adherence of the cells to the dish) LC2 cells could proliferate in the presence of conditioned medium. In addition to this, the fact that Huang et al. demonstrated that cells survive passage and are induced to proliferate in the presence of conditioned media suggests that these cells would survive replating.

Third, with regards to the fact that Huang et al. would motivate one skilled in the art to use conditioned medium over growth medium (and thus be considered a different method step than that of the instant invention), Huang et al. teaches that conditioned media contains a soluble growth factor(s) (Huang et al., page 91, 1st col., 2nd parag.). This is no different from the growth medium taught in the instant specification: "growth medium with which the cells are harvested can comprise a mammalian serum, such as fetal bovine serum, or a growth factor (e.g. fibroblast growth factor, platelet derived growth factor, insulin growth factor, or endothelia growth factor) can be added to the growth medium (specification, page 7, lines 16-19)."

With regards to Huang et al. teaching away from the present invention because one skilled in the art would be motivated to replate the cells at a higher cell density than that recited in the present claims (Applicant's response, page 15, 1st full parag.), the Examiner has calculated that Huang et al. has plated 28 cells per square centimeter (50 cells/1.77cm squared) when cells were plated at 50 cells/well. While the Applicant might argue that Huang et al. does not teach low densities such as 1 cell per square centimeter, the Examiner would point to the fact that Huang et al. overcome the issue, regardless how sparsely cells are plated, by teaching that growth factors induce cells to proliferate. Thus, for this reason, Huang et al. does support a *prima facie* case.

With regards to Huang et al. teaching that a skilled artisan would use the cell line generated by treatment with MPA, the Examiner points Huang et al.'s teaching that MPA kills hemopetic cells and leaves behind stromal cells attached to the flask (Huang et al., page 90, 1st col., 3rd parag.). However, if there is reason to think that the MPA-

treated cells have been altered by the treatment, Huang et al. also teach that LC2 cells, which were not treated with MPA, could also be used.

Thus, for the reasons discussed above, Huang et al.'s teachings make the invention obvious. Claims 1-12, 14-29, 31-36 remain rejected.

Claims 1, 22-29, 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (1997, Biotechnology Letters, 19: 89-92) in view of Kuznetsov et al. (Journal of Bone and Mineral Research, 12: 1335-1347), Azizi et al. (1998, PNAS, USA, 95: 3908-3913), Greenberger et al. (U.S. Patent No. 5,766,950, issue date June 16, 1998), and Prockop (Science, 1997, 276: 71-74) for reasons set forth in the previous Office Action, dated August 10, 2004.

For reasons described above for Huang et al., Huang et al. remains the primary reference for this 103 rejection.

Examiner's Response

Applicant's arguments filed December 27, 2004 have been fully considered but they are not persuasive.

With regards to Kuznetsov et al., while the Applicant correctly points to Kuznetsov et al. teaching a standard culturing methods for a generating a cell population (Kuznetsov et al., page 1337, 1st col., 1st full parag.), the Examiner in the previous Office Action had also pointed to Kuznetsov et al. also teaching a method wherein cells are plated at low density 0.14-14 x 10^3 cells/cm^2 or 0.007-3.5 x 10^3 cells/

cm^2 (Office Action, page 4, 2nd parag.). These cells were grown in media supplemented with 20% fetal bovine serum (Kuznetsov, et al., page 1336, 2nd col., 2nd parag.). While the Applicant discusses the situation regarding propagation of multicolony derived human marrow stromal fibroblast (HMSF) strains, the Applicant does not discuss the plating conditions pointed out by the Examiner regarding low plating conditions in order to obtain single-colony derived HMSF strains.

With regards to Azizi et al., the Examiner used the citation to demonstrate that adding growth factor, PDGF-AA, increased the growth rate of human marrow stromal cells. As Huang et al. teach that the three conditioned media used in the studies could induce LC3 and LC2 cells to proliferate, thus indicating the presence of a soluble growth factor(s), the teachings of Azizi et al., in fact, corroborate Huang et al.'s teaching. Thus, it would have been obvious to an ordinary artisan to use the teachings of Azizi et al. and Huang et al. in order to obtain a method of proliferating sparsely seeded stromal cells.

Similarly, with regards to Greenberger et al., the Examiner used the citation to demonstrate that addition of aFGF and conditioned media (which contains "sufficient nutrients to sustain growth without removing all of the substances secreted by the bone marrow cells, which enhance their growth (Greenberger, et al., col. 6, lines 33-36)." In light of Huang et al. teaching that the three conditioned media used in the studies could induce LC3 and LC2 cells to proliferate, thus indicating the presence of a soluble growth factor(s), the teachings of Greenberger et al., corroborate Huang et al.'s teaching. Thus, it would have been obvious to an ordinary artisan to use the teachings of

Greenberger et al. and Huang et al. in order to obtain a method of proliferating sparsely seeded stromal cells.

With regards to Prockop, the citataion was used to teach that several cytokines were known at the time of filing which were secreted by stromal cells that adhered to culture dishes. While Prockop does not teach low density culturing methods, an artisan of ordinary skill can take the teachings of Huang, et al., wherein Huang et al. teach that conditioned media, which contains a soluble growth factor(s), can be used to induce proliferation in cells plated at low density. For this reason, it would have been obvious to an ordinary artisan to use the teachings of Prockop and Huang et al. in order to obtain a method of proliferating sparsely seeded stromal cells.

For these reasons, the 103 rejection for claims 1, 22-29, 31-36 remain rejected.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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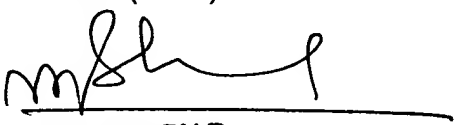
JH



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